INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 27/00, A61C 8/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A61C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5338772 A (HANS-JÖRG BAUER ET AL), 16 August 1994 (16.08.94), column 4, line 66 - column 5, line 18; column 7, line 22 - line 52, abstract, claims	1-17
X	US 4595713 A (KENNETH ST. JOHN), 17 June 1986 (17.06.86), column 6, line 22 - line 45, abstract, claims	1-17
X	EP 0714666 A1 (ETHICON, INC.), 5 June 1996 (05.06.96), page 2 - page 3; page 4, line 18 - line 20; page 4, line 55 - line 60; page 6, line 25 - line 33; page 10, line 16 - line 17; claims; abstract	1-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1998	15 -10- 1998
Name and mailing address of the ISA: Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Monika Bohlin Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0747072 A2 (UNITED STATES SURGICAL CORPORATION), 11 December 1996 (11.12.96), column 3, line 42 - line 46; column 4, line 15 - line 17; column 6, line 14 - line 16, abstract	1-17
A	US 4645503 A (STEVE T. LIN ET AL), 24 February 1987 (24.02.87), column 3, line 23 - line 30; column 4, line 34 - line 41; column 5, line 50 - line 53, abstract, claims	1-17
X	US 5433751 A (PASCAL CHRISTEL ET AL), 18 July 1995 (18.07.95), column 4, line 1 - line 5, claims	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/FI 98/00572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5338772 A	16/08/94	DE 4120325 A	24/12/92
		EP 0519293 A	23/12/92
US 4595713 A	17/06/86	AU 578135 B	13/10/88
		AU 5353086 A	13/08/86
		EP 0210226 A	04/02/87
		JP 62501611 T	02/07/87
		WO 8604235 A	31/07/86
EP 0714666 A1	05/06/96	AU 3795395 A	06/06/96
		BR 9505580 A	04/11/97
		CA 2164045 A	31/05/96
		JP 8215299 A	27/08/96
		US 5679723 A	21/10/97
		US 5747390 A	05/05/98
EP 0747072 A2	11/12/96	CA 2175285 A	08/12/96
		US 5641502 A	24/06/97
US 4645503 A	24/02/87	NONE	
US 5433751 A	18/07/95	AU 667516 B	28/03/96
		AU 3569593 A	07/10/93
		CA 2093269 A	04/10/93
		EP 0564369 A	06/10/93
		FR 2689400 A,B	08/10/93
		JP 6063118 A	08/03/94

18

PATENT COOPERATION TREATY

PCT

REC'D 27 OCT 1999
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ÅP2355	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI98/00572	International filing date *(day/month/year)* 06.07.1998	Priority date *(day/month/year)* 08.07.1997
International Patent Classification (IPC) or national classification and IPC6 A 61 L 27/00, A 61 C 8/00		
Applicant Bioxid Oy et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.1999	18.10.1999
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Monika Bohlin/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI98/00572

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____ , as originally filed,
pages _____ , filed with the demand,
pages _____ , filed with the letter of _____ ,
pages _____ , filed with the letter of _____ .

☐ the claims, Nos. _____ , as originally filed,
Nos. _____ , as amended under Article 19,
Nos. _____ , filed with the demand,
Nos. _____ , filed with the letter of _____ ,
Nos. _____ , filed with the letter of _____ .

☐ the drawings, ~~sheets~~/fig _____ , as originally filed,
~~sheets~~/fig _____ , filed with the demand
~~sheets~~/fig _____ , filed with the letter of _____ ,
~~sheets~~/fig _____ , filed with the letter of _____ .

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI98/00572

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-17	NO
Inventive step (IS)	Claims		YES
	Claims	1-17	NO
Industrial applicability (IA)	Claims	1-17	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to a composite intended for medical use. The composite comprises a thermoplastic component plasticizable within the range -10°C to +100°C, which is made up of hydroxy acids and has the molar mass 10 000- 1 000 000 g/mole. The composite also comprises a bioactive component. The claimed invention also relates to the use of the composite and to products made therefrom.

The following most relevant documents cited in the search report are:

D1 US 5 338 772 A
D2 US 4 595 713 A
D3 EP 0 714 666 A1
D4 US 5 433 751 A

D1 relates to an implant material, which is based on a composite material of calcium phosphate ceramic particles and bioabsorbable polymer. Particularly preferred polymer components in the composite material are polymer materials based on polylactides. The average molecular weight of the polymer material is about 200-10 000 g/mole. The polymer is of hard consistency at room temperature but softens at 40-60 °C

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 relates to a medical implant useful in the regeneration of soft and hard tissue. It comprises a copolymer with 60-95% epsilon caprolactone and 40-5% lactide, it may also include osteogenic material in powdered or particulate form. The average molecular weight of the polymer material is about 200 000-500 000 g/mole. The polymer softens at 46-71°C and is biodegradable.

D3 relates to a biocompatible composite of a first absorbable component comprising a polymer formed from aliphatic lactone monomers selected from, for example, lactide and epsilon caprolactone and a second resorbable component comprising calcium-containing bone regenerating compounds such as powdered calcium phosphate. The average molecular weight of the polymer material is about 5 000- 200 000 g/mole. The polymer softens at temperatures less than 60°C.

D4 finally relates to a bioresorbable bone prosthesis material containing powder of calcium carbonate dispersed within a polymer matrix, where the polymer is a bioresorbable, lactic acid polymer. The weight average molecular mass is at least 40 000 and the material forms a pasty solid at a temperature below 50°C.

The subject matter of claims 1-17 does not differ from the composite described in D2. Consequently, claims 1-17 can not be considered to fulfil the requirements of novelty.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 March 1999 (05.03.99)	
International application No. PCT/FI98/00572	**Applicant's or agent's file reference** ÅP2355
International filing date (day/month/year) 06 July 1998 (06.07.98)	**Priority date** (day/month/year) 08 July 1997 (08.07.97)
Applicant AHO, Allan et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 January 1999 (14.01.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

A. Karkachi

Telephone No.: (41-22) 338.83.38

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61L 27/00, A61C 8/00

A1

(11) International Publication Number: WO 99/02201

(43) International Publication Date: 21 January 1999 (21.01.99)

(21) International Application Number: PCT/FI98/00572

(22) International Filing Date: 6 July 1998 (06.07.98)

(30) Priority Data:
972890 8 July 1997 (08.07.97) FI

(71) Applicants *(for all designated States except US)*: BIOXID OY [FI/FI]; Köydenpunojankatu 2 B 5, FIN–20300 Turku (FI). JVS–POLYMERS OY [FI/FI]; Mäkipellontie 18 C, FIN–00320 Helsinki (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: AHO, Allan [FI/FI]; Yliopistonkatu 1 A 9, FIN–20100 Turku (FI). SEPPÄLÄ, Jukka [FI/FI]; Mäkipellontie 18 C, FIN–00320 Helsinki (FI). YLI–URPO, Antti [FI/FI]; Värttinäkatu 17, FIN–20660 Littoinen (FI). HEIKKILÄ, Jouni [FI/FI]; Vitanovantie 39, FIN–20900 Turku (FI). KANGASNIEMI, Ilkka [FI/FI]; Köydenpunojankatu 2 B 5, FIN–20300 Turku (FI).

(74) Agent: TURUN PATENTTITOIMISTO OY; P.O. Box 99, FIN–20521 Turku (FI).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
In English translation (filed in Finnish).

(54) Title: NOVEL PLASTIC BASED COMPOSITE AND ITS USE

(57) Abstract

The invention relates to a composite intended for medical, in particular surgical or therapeutic, use. According to the invention, the composite comprises a thermoplastic component plasticizable within the temperature range –10 °C ... +100 °C, which is substantially made up of hydroxy acids or structural units derived from hydroxy acid derivatives, and the molar mass of which is within the range 10,000 – 1,000,000 g/mol, and which degrades in the body typically within a period ranging from a few days to several years, and which in its solid state is a mechanically strong plastic or rubbery material, a bioactive component, which is a bioactive glass, a bioactive xerogel, a bioactive ceramic material, coral or a coral–based product, or a bioactive glass ceramic material. The invention also relates to the use of the novel composite and to products made therefrom.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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Published
With international search report.
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NOVEL PLASTIC BASED COMPOSITE AND ITS USE

The invention relates to a composite which contains a plastic-based bioactive component and is intended for medical, in particular surgical or therapeutic, use.

BACKGROUND OF THE INVENTION AND STATE OF THE ART

To elucidate the background of the invention and the state of the art, the publications used, to which reference is made below, are to be viewed as being incorporated into the description of the invention below.

Previously known composites made up of a plastic component and a bioactive component include combinations of hydroxyapatite and methylmethacrylate (literature references (1) - (5)).

However, a thermoplastic, plasticizable at a relatively low temperature, has not been used as the plastic component in the known composites mentioned above.

OBJECT OF THE INVENTION

The object of the invention is to provide a novel composite which is intended for medical use, in particular surgical or therapeutic use, and which contains a thermoplastic component and can be machined and molded into a piece-like, coherent, shock-resistant and load-resistant form.

It is a particular object to provide a composite which can be plasticized at a relatively low temperature.

It is also an object of the invention to provide a composite which is moldable for a certain period even after

its temperature has been lowered to a temperature below the setting temperature of the plastic component.

It is a further object of the invention in particular to provide a composite in which the biodegradability, plasticization temperature and setting rate of the plastic component can be controlled separately.

SUMMARY OF THE INVENTION

The characteristics of the invention are given in Claim 1. A composite according to the invention is characterized in that it comprises

- a thermoplastic component, plasticizable within a temperature range of -10 °C...+100 °C, which is substantially made up of hydroxy acids or structural units derived from hydroxy acid derivatives, which has a molar mass within a range of 10,000 - 1,000,000 g/mol, and which degrades in the body typically within a period ranging from a few days to several years, and which in its solid state is a mechanically strong plastic or rubbery material and
- a bioactive component, which is a bioactive glass, a bioactive xerogel, a bioactive ceramic material, or a bioactive glass ceramic material.

PREFERRED EMBODIMENTS AND A DETAILED DESCRIPTION OF THE INVENTION

The term "medical" is to be understood in the wide meaning of the word and thus also covers dental and veterinary applications.

Bioactive component

By the bioactive component used in the composite according to the present invention is meant a material which reacts in the physiological conditions of the body. The bioactive component may have one or more of the following properties:

bondable to tissues, bioresorbable, bondable/resorbable, releasing active agents, mineralizing, biocompatible, and antimicrobial. The bioactive component is a bioactive glass, a bioactive ceramic material, a bioactive glass ceramic material, coral or a coral-based product, or a bioactive xerogel. The concept of bioactivity is discussed in, for example, Heikkilä's doctoral dissertation (Ref. 1).

In a composite according to the invention, the bioactive component is present as particles separate one from another. The word "particle" here covers particles of different sizes and shapes, such as fibers, solid or porous pieces, rods, microparticles and glass beads.

The bioactive glasses described in references (1) - (5) can be mentioned as examples of suitable bioactive glasses.

Suitable bioactive ceramic materials include Ca phosphates, such as hydroxyapatite.

An especially suitable bioactive component is xerogel. By xerogel is meant a dried gel, which is described in the literature (9, 11). Silica xerogels are partly hydrolyzed oxides of silicon. Hydrolyzed oxide gels can be produced by the sol-gel process, which has been used for the production of ceramic and glass materials for many years.

The sol-gel process is based on the hydrolyzation of metal alkoxides and a subsequent polymerization of the metal hydroxides. As the polymerization reaction progresses, additional chains, rings and three-dimensional networks are formed, and a gel, made up of water, the alcohol of the alkoxy group and the gel itself, is formed. The sol may also contain other additives, such as acids or bases, which are used for the catalysis of the reaction. If the alcohol and the water are removed thereafter from the gel by washing and evaporation, a xerogel is obtained.

The polymerization of the remaining OH groups continues during the drying. The polymerization continues for a long time even after the gelation. This is called aging. The further the polymerization proceeds, the more stable the gel or xerogel becomes. At room temperature, however, the polymerization will in fact stop after an ageing of a few weeks, and the xerogel will not become completely inert. If the temperature is raised, the polymerization reaction can be accelerated, the gel becomes more stable and shrinkage occurs, and internal stresses appear in the xerogel to an increasing degree.

If the temperature is raised to a sufficiently high level (approx. 1000 °C for monolithic silica gels), the gel or xerogel becomes a pure oxide and no OH groups are left in the material. However, in the case of pure oxides, the dissolution reaction rate is very slow. If the oxides are added together with other ions, such as Na, K, Mg or Ca, the reaction rate can be greatly increased. By these methods, bioactive glasses have been developed, which can form a silica gel layer on their surface through an ion exchange reaction. The dissolution rate of these glasses is controlled by the composition and surface area of the glass. The glasses are melted at a temperature above 1000 °C. Therefore it is not possible to add any organic compounds to the structure of the glass.

Sol-Gel glasses have been used, for example, as implant materials, in particular in bone implants (11). These materials do not dissolve completely. The material is formed at a high temperature, and organic compounds cannot be incorporated into its structure. Klein et al. described that when used as implants, silica gels sintered at a lower temperature caused a strong cell reaction in macrophages and in lymphocytes.

Plastic component

The thermoplastic component used in the present invention, plasticizable within a temperature range of -10 °C...+100 °C, may be to a varying degree biodegradable or even bioactive. The term "biodegradable" covers all plastics which are not inert. This group thus includes all bioresorbable plastics (degrading under the action of cells) and biodegradable plastics (degrading under the effect of mere moisture). The use of the composite will determine whether it is expedient to select a plastic which is biodegradable at a slower or a more rapid rate.

Biodegradable types of plastic are suitable for most of the uses of the composite according to the invention. A biodegradable plastic component disappears at the desired rate or is biologically nearly stable, and thus promotes the tissue contact and the desired tissue reaction of the bioactive component. The plastic of the composite thus keeps the particles of the bioactive component in place but does not necessarily prevent the bioactive material from coming into contact with tissue fluid. Since the plastic component gradually decomposes, the water of the tissue fluid comes through diffusion into contact with the bioactive component. Likewise, ions and any active additives released from the bioactive material can become diffused through the plastic and affect their surroundings. The surrounding and/or contact surface tissue grows, filling the void formed by the degradation of the plastic. Ultimately the plastic component decomposes completely and releases any possibly remaining bioactive component.

Alternatively, the plastic component may be nearly inert. A composite made up of a bioactive material and an inert plastic may, if the composite possibly breaks, repair itself in the physiological environment under the mineralizing affect of the bioactive component.

The suitable plasticization temperature (= setting temperature) of the plastic used is also determined according to the intended use of the composite. Plastics plasticizable within a temperature range of 5 °C...70 °C, preferably 37 °C...55 °C, are suited for most of the uses of the composite according to the present invention.

Especially suitable are plastics having a plasticization temperature in the vicinity of body temperature. The application of a product in plastic state will thus not cause thermal damage in the tissue. Also, additives, such as proteins, possibly admixed with the composite would remain undamaged in connection with the preparation and application of the product. If the product implanted in a tissue is required to be soft, it is possible to select a plastic component having a plasticization temperature somewhat lower than body temperature. Such a product can be applied on a hardened form, whereafter it will soften in the tissue.

There are, however, applications in which a very low (down to
-10 °C) setting temperature of the plastic is preferable. One example is a situation in which it is desired to apply a piece or a component therein at a low temperature, whereafter the said piece or component is activated as the temperature rises.

The plasticization temperature of the plastic component can be controlled very precisely, i.e. approx. ±1...±2 °C.

Relatively slowly setting plastics, that is plastics which are moldable for a certain period, i.e. approx. 15 s...30 min, preferably 1...10 min even after the temperature of the plastic has been lowered to a temperature considerably lower than its setting temperature, are especially suitable. By the term "considerably lower" is meant here several degrees Celsius,

suitably approx. 10...15 °C. If the plastic is of a slowly setting type such as this, it is not very critical even if its setting temperature is relatively high, i.e. above 55 °C. The behavior described above is based on the slow mobility of large polymer molecules, in which case setting will occur for some time after the piece has cooled down.

Physiologically suitable types of plastic, plasticizable at a relatively low temperature, are previously known. Poly(ortho esters) (J. Heller, (6, 7)) can be mentioned as an example.

Structure of the polymer:

An especially suitable plastic is a copolymer which is based on structural units such as a hydroxy acid; a hydroxy acid derivative such as a cyclic ester of a hydroxy acid, i.e. lactone; or a cyclic carbonate, such as trimethyl carbonate. L-, D- and DL-lactic acids; L-, D- and DL-lactides; and epsilon-caprolactone are highly suitable structural units.

A plastic component which is a copolymer based on L-lactide and epsilon-caprolactone structural units is especially suitable for this use. The composition of the copolymer typically varies within the range

$$\frac{\text{epsilon-caprolactone}}{\text{L-lactide}} = 2/98 \ldots 98/2$$

and the molar mass M of the copolymer is within the range 10,000...1,000,000 g/mol, suitably within the range 30,000...300,000 g/mol.

It is known that the polymerization of lactones and cyclic carbonates can be carried out by catalytic ring-opening polymerization. The catalyst used may be selected from many

known options, and is typically an organometallic compound, such as tin(II) octoate or triethylaluminum. The control of the molar mass in polymerization of this type is based on an optimal selection of the polymerization temperature and period. It is also possible to use so-called initiator compounds, some typical examples of which are multivalent alcohols such as glycerol. In the polymerization, the polymer chains grow, starting from the -OH groups of the initiator compound, in which case the molar mass will be the lower the larger the amount of initiator present. It is possible to affect the shape of the forming molecule by the structure of the multivalent alcohol. Thus, for example, glycerol forms a comb-like molecule and pentaerythritol a star-like molecule. Polymerization which opens the lactone ring is described in, for example, literature reference (8).

The above-mentioned L-Lactide/epsilon-caprolactone copolymers based on hydroxy acid structural units are described in patent application No. FI 965067.

The control of the melting temperature of the plastic component, i.e. the polymer material, intended for the composite according to the invention is based on one hand on the selection of the monomer ratio in the initial substances and on the other hand on the control of the molar mass in the copolymerization. Both of these factors together affect the melting temperature of the copolymer obtained, and thus only certain combinations produce the desired result. An example of such a composition is a copolymer which contains poly-L-lactide 20 % by weight and ϵ-caprolactone 80 % by weight. If the molar mass of this copolymer is approx. 30,000 g/mol, typically a melting temperature of approx. 40 °C is obtained. If, however, the molar mass of the said copolymer is approx. 300,000 g/mol, a melting temperature of approx. 48 °C is obtained. By the control of the molar mass and the composition, a material with a melting temperature anywhere within the range

-10 °C...+100 °C is obtained.

In many applications, it is desired that the implant material degrades in a controlled manner, or reversely, has mechanical properties that remain stable for at least a certain period. The first stage in the biodegradability of the polymers of the present type is hydrolysis which cuts down the polymer chains until the molecule size is at a level at which the enzymatic functions of the body are capable of converting the degradation products into compounds natural for the body.

In terms of the degradation rate, the hydrophilicity of the polymer is crucial. Thus, in the copolymers being discussed it is possible to control their hydrolytic degradation rate by controlling the monomer composition, and thereby also hydrophilicity, and this, in accordance with what has been stated above, directly affects the degradation of the material in the body.

In terms of the invention, it is essential that, if the composition of the material is solely or almost solely Є-caprolactone, the balance being, for example, L-lactide, DL-lactide, D-lactide or dimethyl carbonate, the polymer is almost stable in the body, or degrades very slowly, typically in the course of a number of years.

By the selection of the monomer composition and the simultaneous control of the average molar mass of the copolymer by means of the preparation parameters, it is possible to exploit the previously known good biocompatibility of polyhydroxy acids. On the other hand, a waxy version of the copolymer material according to the invention can be rendered very rapidly degradable by controlling of the average molar mass and the monomer composition, as presented above. In this case the degradation period in the body is typically from a few days to a few weeks.

The degradation rate of a copolymer which contains poly-L-lactide and ϵ-caprolactone can be controlled by means of the composition, so that when the lactide content is above 60 % by weight, the polymer degrades within a period of less than one month and when the lactide content is below 20 % by weight the degradation period is more than half a year. The degradation rate can be adjusted steplessly between these values by the control of the composition.

The compression resistance of a plastic component in solid state is more than 10 Mpa and its tensile strength at break more than 10 Mpa. The material is plastic or rubbery.

Composite

The plastic component and/or the bioactive component of the composite according to the invention may also contain one or more additives. Examples which can be mentioned of such additives include the elements Ca, Na, P, B, Al, Zn, K, F, Si, Mg, Cl and Ti and their compounds such as oxides; drugs, proteins, proteoglycanes, sugars, growth factors, hormones, enzymes, collagen and antioxidants. It is, of course, the use of the composite that determines the selection of the additive or additives.

The composite according to the invention may form a dense or porous piece. The desired composite structure is obtained by the control of the ratio of the plastic component to the bioactive component. The mixing ratio of the plastic component to the bioactive component can be controlled within quite wide limits, i.e. the concentration of the bioactive component may vary within a range of 1...98 % by weight of the composite. If the concentration of the bioactive component is very high, a composite structure is obtained in which the plastic component forms a binder between the particles of the bioactive component. In this case a rigid composite resembling a sugar lump is obtained. If the concentration of the bioactive component

is lower, i.e. less than 60 % by weight, a plastic-like composite is obtained which may be soft or resilient when so desired.

The composite may be, for example, a coating, membrane, net, thread, fiber, powder, or a piece such as a plate, a bead, a tube, a nail, a rod or an adhesive.

The composite according to the invention may also be prepared in connection with its use, immediately before it is being placed in a tissue (for example, a bone or a tooth). In this case the composite is prepared by "melting" the plastic component and the bioactive component together.

On the basis of the composite according to the invention, it is also possible to prepare a multi-layer composite, such as a multi-layer membrane, so that the plastic components of the different layers plasticize at different temperatures. A multi-layer composite may also be made up of different layers in which the biodegradability of the plastic components is different. The surface layer, or part of the surface layer (one side, one edge area) of an implant made from a multi-layer composite may thus be more rapidly or more slowly biodegradable than the deeper layers of the implant.

The composite according to the invention may also contain holes or channels. Optionally it is also possible to make so-called nutrition channels in the composite during an operation as the composite is being installed.

Applications:

The composite according to the invention can be used for preparing products suited for various uses, some examples being the following groups: bone or cartilage applications, tooth and jaw applications, cartilage coatings and soft tissue applications. Bone applications include, for

example, bone or cartilage filling material, a product intended for repairing long bones, a plate for repairing the back of the eye or facial bones, bone cement, an adhesive for joining the product to a tissue or tissues, an implant coating, a piece for repairing the vertebral column, and a skull plate. Examples of tooth and jaw applications include temporary tooth filling material, temporary or permanent tooth root filling material, a parodontal product, a product to be installed in the cavity remaining after the extraction of a tooth, tooth cement, temporary tooth cement, temporary crown material, tooth implant coating, occlusion index rail, surgical paste and template material, which may be, for example, a paste, ring or thread which is placed in the gingival pocket. A tissue guiding membrane or tube which is applicable to bone, tooth or soft tissue areas can also be mentioned. Further applications include protective cloth, wound dressing, adhesive tape, and a carrier for active agents and other biological structures (autogenic and allogenic bone) and for drugs.

The suitable composite or composites are selected according to the use of the final product.

As to the bioactive component, it can be noted that a composite based on bioactive glass is especially well suited for products which are hoped to promote mineralization (filling materials, tooth coatings, bone fillings, etc.) or which are hoped to form bone bonds for the reconstruction of bone deficiencies (bone fillings, bone cements, various implants, etc.). Composites based on a bioactive gel are especially well suited for final products the purpose of which is to release an active agent (for example, growth factor, hormone, cytostatic, etc.) for the treatment or prevention of a disease. A gel-based composite is also suitable for use in applications in which mineralization and the formation of bone bond are desirable. A gel-based composite is also suitable for the

reinforcement of products (the use of gel fibers for the reinforcement of plastic, bone pins, bone nails and bone screws, membranes, tendon tissue, filling materials, bone fillers, etc.).

The plastic materials may be plastic or rubbery, and their areas of use are divided so that the plastic-like materials will be used mostly for filling purposes and the rubber-like ones mostly for release purposes. Of course, again all types of blends are possible, and the selection of the plastic is mostly determined on the basis of the mechanical requirements.

Bone filler material to be used for the treatment of a fracture of an articular condyle can be taken as an example material. In the treatment of a condyle fracture, the material is required to have sufficient mechanical strength in order for it to be able to support the cortical bone during the healing process. It must be moldable to fill a cavity in the porous bone. It must release inorganic and/or organic compounds promoting bone growth and mineralization for at least the duration of the healing process. Another example is the fracture of a long bone. In the treatment of thé fracture, the material can be used for attaching (gluing) the bone ends in the fracture to each other. A third example is the attaching of small fractured fragments to the parent bone in, for example, a cartilage fracture.

Owing to the requirements presented above, the polymer matrix of a composite material must be plastic and melt to fluid state at approx. 42 °C. Its degradation time should in general be approx. 1 - 6 months, depending on the target 1 - 3 years. The other component of the material must be a sol-gel-produced Ca,P-containing xerogel or a bioactive glass in a granular or fibrous form, in an amount of approx. 60 - 70 % by weight of the material; this promotes the mineralization of the bone and the bonding of the bone to the material. A third component may be a sol-gel-

produced xerogel which contains bone growth factor, promoting bone regeneration in a bone cavity or other bone deficiency.

The following table (Table 1) shows the requirements set on a composite according to the invention as a function of the drug form:

Table 1

	injectable	implantable	needle-like rod-like
polymer matrix	rubbery	plastic or rubbery	plastic
melting temperature	polymer melts at 45° C viscosity low	melting temperature dependent on the drug	melting temperature dependent on the drug
gel	spray-dried beads	particle, fiber or monolith, depending on the shape of the piece	fiber

PREPARATION EXAMPLES

Example 1

Preparation of a matrix polymer

Chemicals used:

The copolymers were prepared from Є-caprolactone monomer (Є-CL), > 99 % pure, Fluka Chemika No. 21510, batch 335334/1 794, and D,L-lactide (D,L-LA), Purac, batch DF386H. The catalyst used was tin(II) octoate (Stannous 2-Ethylhexanoate; SnOct), 95 % pure, Sigma No. s-3252, batch 112H0248. The initiator used was glycerol, 99.5 % pure, Fluka BioChemika No. 49767, batch 42489/2 1094.

Purification and storage of the chemicals used:

There were molecular sieves (added on February 15, 1995) present in the Є-caprolactone used, and the bottle was stored, protected from light, at +23 °C.

The D,L-lactide was purified by recrystallization from toluene (b.p. 110 °C) at a mass ratio of 1:2 toluene/lactide. The lactide dissolved in hot toluene was poured from a round-bottomed flask into a beaker. The lactide dissolved in toluene was allowed to recrystallize overnight at +23 °C. After filtration (medium-rapid filter paper) the crystallized lactide was dried under a lowered pressure for 4 d at +40 °C, the pressure being 4 mbar. The same steps were repeated. Thus, a twice recrystallized D,L-lactide, stored in an exsiccator in a refrigerator at +4 °C, was used in the polymerization runs.

The stannous octoate and glycerol were used as such. They were stored protected from light at +23 °C.

Preliminary preparations for the polymerization:

On the previous evening the lactide to be used for the polymerization was placed in a vacuum chamber at +40 °C under a pressure of 4 mbar. The two-section reactor (volume approx. 0.7 l) required for the polymerization was assembled. In connection with the assembling of the reactor, the condition of the teflon seal of the reactor was checked. The proper closing of the upper and lower sections of the reactor was ensured by using a closing device made from steel wire. Tap grease was applied lightly to the inside upper surfaces of the ground joints of the reactor.

Polymerization:

The oil bath used for the heating of the reactor was adjusted to 140 °C. The temperature of the oil varies during polymerization by 5 °C above and below the setting

value. First, approx. 10 g of the lactide was weighed into a small beaker (precision 0.0001 g). The stannous octoate and the glycerol were weighed and pipetted over the lactide by using a Pasteur pipette. Thereafter the beaker with its contents was poured into the lower section of the reactor. The rest of the lactide was weighed by using another balance (precision 0.01 g). The ϵ-caprolactone was either poured or pipetted over the lactide.

A magnetic stirrer was added to the reactor before the closing of the reactor halves. The reactor was placed in a bath, and the stirring rate was set at 250 min^{-1}. The reactor was rinsed with argon (Aga, quality grade S, 99.99 %) for approx. 15 min. The argon was directed into the reactor via a glycerol lock. Finally the outer surface of the reactor was lined with a foil. The stirring rate was reset at 125 min^{-1} when the forming copolymer began to become more viscous.

Copolymers prepared and their analysis:

Table 2 shows a summary of the ϵ-caprolactone/D,L-lactide (ϵ-CL/D,L-LA) copolymerization runs and the results of the product analyses. In all of the polymerization runs the temperature was 140 °C and the polymerization time 24 h.

The molar mass values of the obtained copolymers, determined by gel permeation chromatography GPC, shown in Table 2, are the number-average molar mass M_n, the weight-average molar mass M_w, and polydispersity PD, obtained as the ratio M_w/M_n of the above values. The same Table 2 shows the melting temperatures T_m, determined by differential scanning calorimetry (DSC), of the polymerization products obtained.

Table 2

Example	ε-CL/ D,L-LA-ratio	SnOct-conc. mol/mol	Glycerol conc. mol/mol	$\overline{M}_n$ 10^{-3} g/mol	$\overline{M}_w$ 10^{-3} g/mol	T_m °C
1	100/0	0,0001	0,005	45	60	56
2	80/20	0,0001	0,005	40	60	42
3	100/0	0,0001	0,25	4,3	5,2	35
4	60/40	0,0001	0,001	20	40	38

Properties of the polymer:

Table 2 shows typical product polymers and their properties.

GPC determinations:

In the determination of the molar mass values by means of GPC, the samples were prepared by dissolving 15 mg of the sample in 10 ml of chloroform. The columns used were columns of Polymer Laboratories Ltd, having a pore size of 10^2 - 10^5 Å. The samples were analyzed by using an RI, i.e. refraction index, detector manufactured by Waters, the run time being 55 min at a flow rate of 1 ml/min. For the determination of the molar masses of the samples, an experimental calibration curve plotted by means of the polystyrene standards (PS) of Polymer Laboratories Ltd was used. Since experimental a-values and K-values of the Mark-Houwink equation are not available for the copolymers, the molar masses in Table 2 are not the absolute molar masses of the samples but relative values, compared with the PS standards.

DSC determinations:

In the DSC determinations, a sample of 5 - 10 g was heated at a rate of 10 °C/min in the calorimeter cell. In order to obtain the same thermal history for all of the samples, the samples were heated above their melting temperature, to a temperature above +80 °C, and were cooled to approx. -50 °C. The T_m values, shown in Table 2, were registered from the curve of the second heating.

Example 2

Preparation of a composite material

An amount of 20 g of a polymer prepared according to Example 1 was taken. An amount of 20 g of a bioactive glass (type S53P4, reference 10) having an average particle size of 300 µm was taken. The components were poured into the Kneteter mixing head of a Brabender Co-Kneader apparatus, where the rotation speed was 50 rpm. The temperature of the Kneteter head had been set at 55 °C, and the mixing time was 15 min, whereafter the mixing head was opened and the homogenized material was recovered in a molten state.

The final product obtained was a homogeneous composite material having a bioglass content of 50 % by weight. The composite was stored in a gas-tight vessel under nitrogen shield gas.

The above embodiments of the invention are only examples of the implementation of the idea according to the invention. For a person skilled in the art it is clear that the various embodiments of the invention may vary within the claims presented below.

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CLAIMS

1. A composite intended for medical use, in particular surgical or therapeutic use, characterized in that it comprises
- a thermoplastic component plasticizable within the temperature range -10 °C...+100 °C, which is substantially made up of hydroxy acids and structural units derived from hydroxy acid derivatives, and the molar mass of which is within the range 10,000 - 1,000,000 g/mol, and which degrades in the body typically within a period ranging from a few days to several years, and which in its solid state is a mechanically strong plastic or rubbery material, and
- a bioactive component, which is a bioactive glass, a bioactive xerogel, a bioactive ceramic material, coral or a coral-based product, or a bioactive glass ceramic material.

2. The composite according to Claim 1, characterized in that the plastic component is plasticizable within the temperature range 5 °C...70 °C, preferably within the temperature range 37 °C...55 °C.

3. The composite according to Claim 1 or 2, characterized in that the plasticized plastic component remains moldable for a certain period even after the temperature of the composite has been lowered to a temperature which is considerably lower than the setting temperature of the said plastic component.

4. The composite according to Claim 1, 2 or 3, characterized in that the plastic component is biodegradable in a controlled manner within the time range 1 week - 3 years.

5. The composite according to Claim 4, characterized in that the structural unit is an L-, D- or DL-lactic acid; an L-, D- or DL-lactide; or epsilon-caprolactone.

6. The composite according to Claim 5, characterized in that the plastic component is a copolymer based on structural units of L-lactide and epsilon-caprolactone.

7. The composite according to Claim 6, characterized in that the composition of the copolymer is within the range

$$\frac{\text{epsilon-caprolactone}}{\text{L-lactide}} = 2/98 \ldots 98/2$$

8. The composite according to Claim 7, characterized in that

$$\frac{\text{epsilon-caprolactone}}{\text{L-lactide}} = 4 : 1$$

9. The composite according to Claim 8, characterized in that the molar mass of the copolymer is approx. 30,000 - 300,000 g/mol.

10. The composite according to any of the above claims, characterized in that the bioactive component is present as separate particles in the composite.

11. The composite according to Claim 10, characterized in that the separate particles are fibers, porous pieces, microparticles or glass beads.

12. The composite according to any of the above claims, characterized in that the plastic component and/or the bioactive component contains one or more additives.

13. The composite according to any of the above claims, characterized in that the plastic component and the bioactive component form a dense piece.

14. The composite according to any of Claims 1 - 12,

characterized in that the plastic component forms a porous piece.

15. A blend intended for the preparation of a composite according to any of Claims 1 - 14, characterized in that the plastic component and the bioactive component in the blend are in powder form.

16. A coating, membrane, net, powder, fiber, thread, adhesive, or a piece such as a plate, bead, tube, nail or rod, prepared from the composite according to any of Claims 1 - 14.

17. The use of a composite according to any of Claims 1 - 14 for the preparation of any of the following products:
- a bone or cartilage application, such as a filling material for bone or cartilage, a product intended for the repairing of long bones, a plate for the repairing of the back of the eye or facial bones, a bone cement, an adhesive for joining the product to a tissue or tissues, an implant coating, a piece for the repairing of the vertebral column, and a skull plate,
- a tooth or jaw application, such as a temporary tooth filling material, a temporary or permanent tooth root filling material, a parodontal product, a product to be placed in the cavity left by an extracted tooth, a tooth cement, a temporary tooth cement, a temporary crown material, a tooth implant coating, an occlusion index rail, a surgical paste, and a template material, which may be, for example, a paste, ring or thread to be fitted in a gingival pocket,
- a cartilage coating,
- a tissue guiding membrane or tube,
- a protective cloth, a wound dressing, or an adhesive tape,
- a carrier for an active agent, such as a drug, or for some other biological structure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 27/00, A61C 8/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A61C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5338772 A (HANS-JÖRG BAUER ET AL), 16 August 1994 (16.08.94), column 4, line 66 - column 5, line 18; column 7, line 22 - line 52, abstract, claims --	1-17
X	US 4595713 A (KENNETH ST. JOHN), 17 June 1986 (17.06.86), column 6, line 22 - line 45, abstract, claims --	1-17
X	EP 0714666 A1 (ETHICON, INC.), 5 June 1996 (05.06.96), page 2 - page 3; page 4, line 18 - line 20; page 4, line 55 - line 60; page 6, line 25 - line 33; page 10, line 16 - line 17; claims; abstract --	1-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw douhts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0747072 A2 (UNITED STATES SURGICAL CORPORATION), 11 December 1996 (11.12.96), column 3, line 42 - line 46; column 4, line 15 - line 17; column 6, line 14 - line 16, abstract --	1-17
A	US 4645503 A (STEVE T. LIN ET AL), 24 February 1987 (24.02.87), column 3, line 23 - line 30; column 4, line 34 - line 41; column 5, line 50 - line 53, abstract, claims --	1-17
X	US 5433751 A (PASCAL CHRISTEL ET AL), 18 July 1995 (18.07.95), column 4, line 1 - line 5, claims -- --------	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/FI 98/00572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5338772 A	16/08/94	DE 4120325 A	24/12/92
		EP 0519293 A	23/12/92
US 4595713 A	17/06/86	AU 578135 B	13/10/88
		AU 5353086 A	13/08/86
		EP 0210226 A	04/02/87
		JP 62501611 T	02/07/87
		WO 8604235 A	31/07/86
EP 0714666 A1	05/06/96	AU 3795395 A	06/06/96
		BR 9505580 A	04/11/97
		CA 2164045 A	31/05/96
		JP 8215299 A	27/08/96
		US 5679723 A	21/10/97
		US 5747390 A	05/05/98
EP 0747072 A2	11/12/96	CA 2175285 A	08/12/96
		US 5641502 A	24/06/97
US 4645503 A	24/02/87	NONE	
US 5433751 A	18/07/95	AU 667516 B	28/03/96
		AU 3569593 A	07/10/93
		CA 2093269 A	04/10/93
		EP 0564369 A	06/10/93
		FR 2689400 A,B	08/10/93
		JP 6063118 A	08/03/94

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 27/00, A61C 8/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A61C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5338772 A (HANS-JÖRG BAUER ET AL), 16 August 1994 (16.08.94), column 4, line 66 - column 5, line 18; column 7, line 22 - line 52, abstract, claims --	1-17
X	US 4595713 A (KENNETH ST. JOHN), 17 June 1986 (17.06.86), column 6, line 22 - line 45, abstract, claims --	1-17
X	EP 0714666 A1 (ETHICON, INC.), 5 June 1996 (05.06.96), page 2 - page 3; page 4, line 18 - line 20; page 4, line 55 - line 60; page 6, line 25 - line 33; page 10, line 16 - line 17; claims; abstract --	1-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw douhts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1998	15 -10- 1998
Name and mailing address of the ISA: Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Monika Bohlin Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 98/00572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0747072 A2 (UNITED STATES SURGICAL CORPORATION), 11 December 1996 (11.12.96), column 3, line 42 - line 46; column 4, line 15 - line 17; column 6, line 14 - line 16, abstract --	1-17
A	US 4645503 A (STEVE T. LIN ET AL), 24 February 1987 (24.02.87), column 3, line 23 - line 30; column 4, line 34 - line 41; column 5, line 50 - line 53, abstract, claims --	1-17
X	US 5433751 A (PASCAL CHRISTEL ET AL), 18 July 1995 (18.07.95), column 4, line 1 - line 5, claims -- --------	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/FI 98/00572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5338772 A	16/08/94	DE 4120325 A	24/12/92
		EP 0519293 A	23/12/92
US 4595713 A	17/06/86	AU 578135 B	13/10/88
		AU 5353086 A	13/08/86
		EP 0210226 A	04/02/87
		JP 62501611 T	02/07/87
		WO 8604235 A	31/07/86
EP 0714666 A1	05/06/96	AU 3795395 A	06/06/96
		BR 9505580 A	04/11/97
		CA 2164045 A	31/05/96
		JP 8215299 A	27/08/96
		US 5679723 A	21/10/97
		US 5747390 A	05/05/98
EP 0747072 A2	11/12/96	CA 2175285 A	08/12/96
		US 5641502 A	24/06/97
US 4645503 A	24/02/87	NONE	
US 5433751 A	18/07/95	AU 667516 B	28/03/96
		AU 3569593 A	07/10/93
		CA 2093269 A	04/10/93
		EP 0564369 A	06/10/93
		FR 2689400 A,B	08/10/93
		JP 6063118 A	08/03/94

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ÅP2355	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI98/00572	International filing date *(day/month/year)* 06.07.1998	Priority date *(day/month/year)* 08.07.1997
International Patent Classification (IPC) or national classification and IPC6 A 61 L 27/00, A 61 C 8/00		
Applicant Bioxid Oy et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.1999	18.10.1999
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Authorized officer Monika Bohlin/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI98/00572

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI98/00572

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-17	NO
Inventive step (IS)	Claims		YES
	Claims	1-17	NO
Industrial applicability (IA)	Claims	1-17	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to a composite intended for medical use. The composite comprises a thermoplastic component plasticizable within the range -10°C to +100°C, which is made up of hydroxy acids and has the molar mass 10 000- 1 000 000 g/mole. The composite also comprises a bioactive component. The claimed invention also relates to the use of the composite and to products made therefrom.

The following most relevant documents cited in the search report are:

D1 US 5 338 772 A
D2 US 4 595 713 A
D3 EP 0 714 666 A1
D4 US 5 433 751 A

D1 relates to an implant material, which is based on a composite material of calcium phosphate ceramic particles and bioabsorbable polymer. Particularly preferred polymer components in the composite material are polymer materials based on polylactides. The average molecular weight of the polymer material is about 200-10 000 g/mole. The polymer is of hard consistency at room temperature but softens at 40-60 °C

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 relates to a medical implant useful in the regeneration of soft and hard tissue. It comprises a copolymer with 60-95% epsilon caprolactone and 40-5% lactide, it may also include osteogenic material in powdered or particulate form. The average molecular weight of the polymer material is about 200 000-500 000 g/mole. The polymer softens at 46-71°C and is biodegradable.

D3 relates to a biocompatible composite of a first absorbable component comprising a polymer formed from aliphatic lactone monomers selected from, for example, lactide and epsilon caprolactone and a second resorbable component comprising calcium-containing bone regenerating compounds such as powdered calcium phosphate. The average molecular weight of the polymer material is about 5 000- 200 000 g/mole. The polymer softens at temperatures less than 60°C.

D4 finally relates to a bioresorbable bone prosthesis material containing powder of calcium carbonate dispersed within a polymer matrix, where the polymer is a bioresorbable, lactic acid polymer. The weight average molecular mass is at least 40 000 and the material forms a pasty solid at a temperature below 50°C.

The subject matter of claims 1-17 does not differ from the composite described in D2. Consequently, claims 1-17 can not be considered to fulfil the requirements of novelty.

RECORD COPY

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/FI 9 8 / 0 0 5 7 2
International Application No.

International Filing Date 06 JUL 1998 (06. 07. 98)

The Finnish Patent Office
PCT International Application
Name of receiving Office and "PCT International Application"

~~Applicant's or~~ agent's file reference
(if desired) (12 characters maximum) ÅP2355

Box No. I TITLE OF INVENTION

Novel plastic based composite and its use

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BIOXID OY
~~[c/o Ilkka Kangasniemi]~~
Köydenpunojankatu 2 B 5
FIN-20300 Turku
Finland

ΔΔ DELETED BY RO/FI

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

JVS-POLYMERS OY
Mäkipellontie 18 C
FIN-00320 Helsinki
Finland

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Turun Patenttitoimisto Oy
P.O. Box 99
FIN-20521 Turku
Finland

Telephone No.
+358 2 274 1555

Facsimile No.
+358 2 274 1556

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AHO, Allan
Yliopistonkatu 1 A 9
FIN-20100 Turku
Finland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SEPPÄLÄ, Jukka
Mäkipellontie 18 C
FIN-00320 Helsinki
Finland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YLI-URPO, Antti
Värttinäkatu 17
FIN-20660 Littoinen
Finland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HEIKKILÄ, Jouni
Vitanovantie 39
FIN-20900 Turku
Finland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. 3 PC /FI98/00572

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KANGASNIEMI, Ilkka
Köydenpunojankatu 2 B 5
FIN-20300 Turku
Finland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: FI

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus .....
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
- ☒ EE Estonia .....
- ☒ ES Spain .....
- ☒ FI Finland .....
- ☒ GB United Kingdom
- ☒ GE Georgia .....
- ☒ GH Ghana .....
- ☒ GM Gambia
- ☒ GW Guinea-Bissau .....
- ☒ HR Croatia
- ☒ HU Hungary .....
- ☒ ID Indonesia
- ☒ IL Israel .....
- ☒ IS Iceland
- ☒ JP Japan .....
- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakhstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 8 July 1997 (08.07.97)	972890	FI		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	5
description (excluding sequence listing part)	:	19
claims	:	3
abstract	:	1
drawings	:	-
sequence listing part of description	:	-
Total number of sheets	:	28

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: copy of Official Action

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: Finnish

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

TURUN PATENTTITOIMISTO OY

Ann-Marie Öhman
Patent attorney

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1. Date of actual receipt of the purported international application: 06 JUL 1998 (06-07-1998)
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /SE
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau: 04 AUGUST 1998 (04.08.98)

UUSI MUOVIPOHJAINEN KOMPOSIITTI JA SEN KÄYTTÖ

Keksinnön kohteena on lääketieteelliseen, erityisesti kirurgiseen tai terapeuttiseen käyttöön tarkoitettu, muovipohjaista, bioaktiivista komponenttia sisältävä komposiitti.

KEKSINNÖN TAUSTA JA TEKNIIKAN TASO

Keksinnön taustan ja tekniikan tason valaisemiseksi käytettyjen julkaisujen, joihin jatkossa on viitattu, on katsottava sisältyvän alla esitettyyn keksinnön kuvaukseen.

Ennestään tunnettuja muovikomponentista ja bioaktiivisesta komponentista koostuvia komposiitteja ovat esimerkiksi hydroksiapatiitin ja metyylimeta-akrylaatin yhdistelmät (kirjallisuusviitteet (1) - (5)).

Yllä mainittujen tunnettujen komposiittien muovikomponenttina ei ole kuitenkaan käytetty verraten alhaisessa lämpötilassa plastisoitavissa olevaa termoplastista muovia.

KEKSINNÖN TARKOITUS

Keksinnön tarkoituksena on aikaansaada uusi lääketieteelliseen käyttöön, erityisesti kirurgiseen tai terapeuttiseen käyttöön soveltuva, termoplastista muovikomponenttia sisältävä komposiitti, joka on työstettävä ja muovailtava kappalemaiseen, koossapysyvään, iskulujaan ja kuormitusrasitusta kestävän muotoon.

Erityisesti on tarkoituksena aikaansaada komposiitti, joka on plastisoitavissa verraten alhaisessa lämpötilassa.

Keksinnön tarkoituksena on myös aikaansaada komposiitti, joka on muovailtavissa tietyn ajan vielä sen jälkeen, kun sen lämpötila on laskettu muovikomponentin kovettumislämpö-

tilan alapuolelle.

Keksinnön tarkoituksena on edelleen erityisesti aikaansaada sellainen komposiitti, jonka muovikomponentin biohajoavaisuus, plastisointilämpötila ja kovettumisnopeus ovat säädettävissä erikseen.

YHTEENVETO KEKSINNÖSTÄ

Keksinnön tunnusmerkit ilmenevät patenttivaatimuksesta 1. Keksinnön mukaiselle komposiitille on tunnusomaista, että se käsittää
- lämpötila-alueella -10 °C...+100°C plastisoitavissa olevan termoplastisen muovikomponentin, joka oleellisesti koostuu hydroksihapoista tai hydroksihappojohdannaisista johdetuista rakenneyksiköistä, ja jonka moolimassa on alueella 10 000 - 1 000 000 g/mol, ja joka hajoaa elimistössä tyypillisesti muutamasta päivästä usemapiin vuosiin pituisessa ajassa ja joka kiinteässä muodossaan on mekaanisesti luja muovimainen tai kumimainen aine, sekä
- bioaktiivisen komponentin, joka on bioaktiivinen lasi, bioaktiivinen xerogeeli, bioaktiivinen keraami tai bioaktiivinen lasikeraami.

KEKSINNÖN SUOSITELTAVAT SUORITUSMUODOT JA SEIKKAPERÄINEN KUVAUS

Käsite "lääketieteellinen" on ymmärrettävä sanan laajassa merkityksessä ja kattaa näin ollen myös hammaslääketieteelliset ja eläinlääketieteelliset sovellukset.

Bioaktiivinen komponentti

Tämän keksinnön mukaisessa komposiitissa käytetyllä bioaktiivisella komponentilla tarkoitetaan sellaista materiaalia, joka reagoi elimistön fysiologisissa olosuhteissa. Bioaktiivisella komponentilla voi olla yksi tai useampia seuraavista ominaisuuksista: kudoksiin sitoutuva, bioresor-

boituva, sitoutuva/resorboituva, vaikuttavia aineita vapauttava, mineralisoiva, bioyhteensopiva/compatible ja antimikrobielli. Bioaktiivinen komponentti on bioaktiivinen lasi, bioaktiivinen keraami, bioaktiivinen lasikeraami, koralli tai koralliperäinen tuote, tai bioaktiivinen xerogeeli. Bioaktiivisuuden käsitettä on käsitelty mm. Heikkilän väitöskirjassa (viite 1).

Keksinnön mukaisessa komposiitissa bioaktiivinen komponentti esiintyy toisistaan erillisinä partikkeleina. Sana "partikkeli" kattaa tässä erikokoisia ja -muotoisia partikkeleita, kuten kuituja, kiinteitä tai huokoisia kappaleita, sauvoja, mikropartikkeleita tai lasipalloja.

Sopivista bioaktiivisista laseista voidaan mainita viitteissä (1) - (5) kuvattuja bioaktiivisia laseja.

Sopivia bioaktiivisia keraameja ovat esimerkiksi Ca-fosfaatit, kuten hydroksiapatiitti.

Erityisen sopiva bioaktiivinen komponentti on xerogeeli. Xerogeelillä tarkoitetaan kuivattua geeliä, joka on kuvattu kirjallisuudessa (9, 11). Pii-xerogeelit ovat osittain hydrolysoituja piin oksideja. Hydrolysoituja oksidigeelejä voidaan tuottaa sol-gel -prosessilla, jota on käytetty keraamisten ja lasimateriaalien tuottamiseen monta vuotta.

Sol-gel -prosessi perustuu metallialkoksidien hydrolysaatioon ja sitä seuraavaan metallihydroksidien polymerisaatioon.

Kun polymerisaatioreaktio etenee, lisää ketjuja, renkaita ja kolmiulotteisia verkkoja syntyy ja muodostuu geeli, joka koostuu vedestä, alkoksiryhmän alkoholista ja itse geelistä. Sooli voi myöskin sisältää muita lisäaineita kuten happoja tai emäksiä, joita käytetään reaktion katalyysiin. Jos alkoholi ja vesi poistetaan tämän jälkeen geelistä pesemällä ja haihduttamalla saadaan xerogeeli.

Kuivauksen aikana jatkuu jäljelle jääneiden OH -ryhmien polymerisaatio. Polymerisaatio jatkuu pitkään geelin muodostuksen jälkeenkin. Tätä kutsutaan kypsymiseksi. Mitä pitemmälle polymerisaatio etenee, sitä stabiilimmaksi geeli tai xerogeeli tulee. Huoneen lämpötilassa polymerisaatio kuitenkin itseasiassa loppuu muutaman viikon kypsymisen jälkeen ja xerogeelistä ei tule täysin inerttiä. Jos lämpötilaa nostetaan, polymerisaatioreaktiota voidaan kiihdyttää, geelistä tulee stabiilimpi ja kutistumista tapahtuu, ja xerogeeliin tulee enenevässä määrin sisäistä jännitystä.

Jos lämpötila nostetaan riittävän korkealle (noin 1000 °C monoliittisille piigeeleille) geelistä tai xerogeelistä tulee puhdas oksidi ja aineessa ei ole enää OH -ryhmiä jäljellä. Tosin, kun on kyse puhtaista oksideista, on liukenemisen reaktionopeus erittäin hidas. Jos oksidit lisätään yhdessä muiden ionien kuten Na, K , Mg tai Ca kanssa, reaktionopeutta voidaan lisätä paljon. Näillä menetelmillä on kehitetty bioaktiiviset lasit, jotka voivat muodostaa piigeelikerroksen pinnalleen ioninvaihtoreaktion kautta. Näiden lasien liukenemisnopeus säädetään lasin koostumuksen ja pinta-alan avulla. Lasit sulatetaan yli 1000 °C lämpötilassa. Siksi ei ole mahdollista lisätä mitään orgaanisiä yhdisteitä lasin rakenteeseen.

Sol-gel -laseja on käytetty mm. implanttimateriaaleina, etenkin luustoimplantteihin (11). Nämä materiaalit eivät liukene täydellisesti. Aine on muodostettu korkeassa lämpötilassa eikä orgaanisia yhdisteitä voida sisällyttää sen rakenteeseen. Klein et al. kuvasi, että alemmassa lämpötilassa sintratut silikageelit aikaansaivat voimakkaan solureaktion makrofageissa ja lymfosyyteissa kun niitä käytettiin implantteina.

Muovikomponentti

Tässä keksinnössä käytetty lämpötila-alueella -10 °C...+100 °C plastisoitavissa oleva termoplastinen

muovikomponentti voi olla vaihtelevassa määrin biohajoava tai jopa bioaktiivinen. Käsite "biohajoava" kattaa kaikki muovit, jotka eivät ole inerttejä. Tähän ryhmään kuuluvat siten bioresorboituvat muovit (solujen vaikutuksesta hajoavat) ja biodegradoituvat muovit (pelkästään kosteuden vaikutuksesta hajoavat muovit). Komposiitin käyttötarkoitus määrää sen, onko tarkoituksenmukaista valita hitaammin vai nopeammin bioahajoava muovi.

Biohajoavat muovityypit soveltuvat useimpiin keksinnön mukaisen komposiitin käyttötarkoituksiin. Biohajoava muovikomponentti häviää halutulla nopeudella tai on biologisesti lähes pysyvä, ja edesauttaa täten bioaktiivisen komponentin kudoskontaktia ja toivottua kudosreaktiota. Komposiitin muovi pitää tällöin bioaktiivisen komponentin partikkelit paikoillaan, mutta se ei kuitenkaan välttämättä estä bioaktiivista materiaalia tulemasta kosketukseen kudosnesteen kanssa. Koska muovikomponentti vähitellen hajoaa, pääsee kudosnesteen vesi diffuusion kautta kosketukseen bioaktiivisen komponentin kanssa. Samoin pääsevät bioaktiivisesta materiaalista vapautuneet ionit ja mahdolliset vaikuttavat lisäaineet diffundoitumaan muovin läpi ja vaikuttamaan ympäristöönsä. Ympäröivä ja/tai kontaktipinnan kudos kasvaa täyttäen muovin hajoamisesta muodostuvan tyhjän tilan. Lopulta muovikomponentti hajoaa kokonaan ja vapauttaa mahdollisen jäljellä olevan bioaktiivisen komponentin.

Muovikomponentti voi vaihtoehtoisesti olla lähes inertti. Komposiitti, joka koostuu bioaktiivisesta materiaalista ja inertistä muovista, voi komposiitin mahdollisesti murtuessa fysiologisessa ympäristössä korjata itsensä bioaktiivisen komponentin mineralisoivan vaikutuksen ansiosta.

Käytetyn muovin sopiva plastisointilämpötila (= kovettumislämpötila) määräytyy myös komposiitin käyttötarkoituksen mukaan. Lämpötila-alueella 5 °C...70 °C, edullisesti 37 °C...55 °C plastisoitavissa olevat muovit soveltuvat useimpiin tämän keksinnön mukaisen komposiitin käyttötarkoituk-

siin.

Erityisen sopivia ovat sellaiset muovit, joiden plastisointilämpötila on ruumiinlämpötilan läheisyydessä. Plastisessa tilassa olevan tuotteen asettaminen paikalleen ei täten aiheuta lämpövaurioita kudokseen. Myöskin komposiittiin mahdollisesti seostetut lisäaineet kuten proteiinit säilyisivät vahingoittumattomina tuotteen valmistuksen ja applikaation yhteydessä. Jos kudokseen asetetun tuotteen tulisi olla pehmeä, voidaan valita sellainen muovikomponentti, jonka plastisointilämpötila on hieman alempi kuin ruumiin lämpötila. Tällainen tuote voidaan applikoida kovetetussa muodossa, minkä jälkeen se pehmenee kudoksessa.

On kuitenkin olemassa sovelluksia, joissa muovin hyvin alhainen (jopa -10 °C) kovettumislämpötila on suositeltava. Esimerkkinä voidaan mainita tilanne, jossa halutaan applikoida kappale tai siinä oleva komponentti alhaisessa lämpötilassa, minkä jälkeen mainittu kappale tai komponentti aktivoituu lämpötilan noustessa.

Muovikomponentin plastisointilämpötila voidaan säätää hyvin tarkasti, eli noin ±1...±2 °C.

Erityisen sopivia ovat verraten hitaasti kovettuvat muovit, so. sellaiset, jotka ovat muovailtavissa tietyn ajan, eli noin 15 s...30 min, edullisesti 1...10 min vielä sen jälkeen, kun muovin lämpötila on laskettu tuntuvasti alempaan lämpötilaan kuin sen kovettumislämpötila. Käsitteellä "tuntuvasti alempi" tarkoitetaan tässä useita celsiusasteita, sopivasti noin 10...15 °C. Jos muovi on tällainen hitaasti koveneva, ei ole niin kriittistä, vaikka sen kovettumislämpötila olisi suhteellisen korkea, eli yli 55 °C. Edellä kuvattu käyttäytyminen perustuu suurten polymeerimolekyylien hitaaseen liikkuvuuteen, jolloin kovettumista tapahtuu jonkin aikaa kappaleen jäähdyttyä.

Fysiologisesti sopivat, verraten matalassa lämpötilassa

plastisoitavissa olevia muovityyppeja ovat ennestään tunnettuja. Esimerkkinä voidaan mainita polyortoesterit (J Heller, (6,7)).

Polymeerin rakenne:

Erityisen sopiva muovi on sekapolymeeri, joka perustuu sellaisiin rakenneyksiköihin kuin jokin hydroksihappo; hydroksihappojohdannainen, kuten esimerkiksi hydroksihapon syklinen esteri eli laktoni; tai syklinen karbonaatti kuten esimerkiksi trimetyylikarbonaatti. Varsin sopivia rakenneyksiköitä ovat L-, D- tai DL-maitohappo; L-, D- tai DL-laktidi; tai epsilon-kaprolaktoni.

Erityisen soveltuva tähän käyttötarkoitukseen on muovikomponentti, joka on L-laktidi- ja epsilon-kaprolaktoni-rakenneyksiköihin perustuva sekapolymeeri. Sekapolymeerin koostumus vaihtelee tyypillisesti alueella

$$\frac{\text{epsilon-kaprolaktoni}}{\text{L-laktidi}} = 2/98 \ldots 98/2$$

ja sekapolymeerin moolimassa M on alueella 10 000...1 000 000 g/mol, sopivasti alueella 30 000...300 000 g/mol.

Laktonien ja syklisten karbonaattien polymerointi voidaan tunnetusti tehdä katalyyttisellä renkaan avaavalla polymeroinnilla. Käytettävä katalyytti voidaan valita monista tunnetuista vaihtoehdoista ja on tyypillisesti jokin organometallinen yhdiste kuten tina(II)oktoaatti tai trietyylialumiini. Moolimassan säätö tämän tyyppisessä polymeroinnissa perustuu polymerointilämpötilan ja -ajan optimaaliseen valintaan. On myös mahdollista käyttää nk. initiaattoriyhdisteitä, joista tyypillisiä ovat moniarvoiset alkoholit kuten glyseroli. Polymeroinnissa polymeeriketjut kasvavat initiaattoriyhdisteen -OH -ryhmistä lähtien, jolloin moolimassasta tulee sitä alhaisempi mitä enemmän

initiaattoria on läsnä. Moniarvoisen alkoholin rakenteella voidaan vaikuttaa muodostuvan molekyylin muotoon. Näin esimerkiksi glyseroli muodostaa kampamaisen ja pentaerytritoli tähtimäisen molekyylin. Laktonien renkaan avaava polymerointi on kuvattu esimerkiksi kirjallisuusviitteessä (8).

Edellä mainitut hydroksihapporakenneyksiköihin perustuvat L-laktidi/epsilon-kaprolaktoni -sekapolymeerit on kuvattu patenttihakemuksessa nro FI 965067.

Keksinnön mukaiseen komposiittiin tarkoitetun muovikomponentin eli polymeerimateriaalin sulamislämpötilan säätö perustuu toisaalta monomeerisuhteen valintaan lähtöaineissa, ja toisaalta moolimassan säätöön kopolymeroinnissa. Molemmat seikat yhdessä vaikuttavat saadun kopolymeerin sulamislämpötilaan, joten vain tietyt kombinaatiot tuottavat halutun tuloksen. Tällainen koostumus on esimerkiksi poly-L-laktidia 20 p-% ja ϵ-kaprolaktonia 80 p-% sisältävä sekapolymeeri. Jos tämän sekapolymeerin moolimassa on noin 30 000 g/mol saavutetaan tyypillisesti sulamislämpötila, joka on noin 40 °C. Jos mainitun sekapolymeerin moolimassa taas on noin 300 000 g/mol saadaan sulamislämpötil, joka on noin 48 °C. Säätämällä moolimassaa ja koostumusta saadaan materiaali, jonka sulamislämpötila on mikä tahansa välillä -10 °C...+100 °C.

Useissa sovelluksissa halutaan implanttimateriaalin olevan kontrolloidusti hajoavaa, tai kääntäen ainakin tietyn ajan mekaanisilta ominaisuuksiltaan pysyvä. Nyt puheena olevaa tyyppiä olevien polymeerien biohajoavuuden ensimmäinen vaihe on hydrolyysi, joka pilkkoo polymeeriketjut pienemmiksi, kunnes molekyylikoko on tasolla, jolla elimistön omat entsymaattiset toiminnot voivat muuttaa hajoamistuotteet elimistölle luonnollisiksi yhdisteiksi.

Hajoamisnopeuden kannalta polymeerin hydrofiilisyys on keskeinen seikka. Niinpä puheena olevissa kopolymeereissä

monomeerikoostumusta, ja siten myös hydrofiilisyyttä, säätämällä on mahdollista säädellä hydrolyyttistä hajoamisnopeutta, mikä edellä esitetyn mukaisesti suoraan vaikuttaa materiaalin hajoamiseen elimistössä.

Oleellista keksinnön kannalta on, että mikäli materiaalin koostumus on yksinomaan tai lähes yksinomaan ϵ-kaprolaktonia, lopun ollessa esim. L-laktidia, DL-laktidia, D-laktidia tai dimetyylikarbonaattia, on polymeeri elimistössä lähes pysyvä, tai hyvin hitaasti, tyypillisesti usean vuoden kuluessa hajoava.

Valitsemalla monomeerikoostumus ja samanaikaisesti säätämällä valmistusparametrien avulla kopolymeerin keskimääräistä moolimassaa voidaan hyödyntää polyhydroksihappojen tunnetusti hyvää bioyhteensopivuutta. Toisaalta vahamainen versio keksinnön mukaisesta kopolymeerimateriaalista voidaan saada hyvinkin nopeasti hajoavaksi keskimääräistä moolimassaa ja monomeerikoostumusta säätämällä kuten edellä on esitetty. Tällöin hajoamisaika elimistössä on tyypillisesti joistakin päivistä joihinkin viikkoihin.

Poly-L-laktidia ja ϵ-kaprolaktonia sisältävä sekapolymeerin hajoavuusnopeutta voidaan säätää koostumuksen avulla siten, että laktidipitoisuuden ollessa yli 60 p-% polymeeri on hajoava alle yhden kuukauden ajassa, ja laktidipitoisuuden ollessa alle 20 p-% hajoamisaika on yli puoli vuotta. Hajoamisnopeus on portaattomasti säädettävissä näiden arvojen välillä koostumusta säätämällä.

Kiinteässä muodossa olevan muovikomponentin puristuslujuus on yli 10 Mpa ja vetomurtolujuus yli 10 Mpa. Materiaali on olomuodoltaan muovimainen tai kumimainen.

Komposiitti

Keksinnön mukainen komposiitin muovikomponentti ja/tai bioaktiivinen komponentti voi myös sisältää yhden tai

useamman lisäaineen. Esimerkkeinä sellaisista lisäaineista voidaan mainita alkuaineet Ca, Na, P, B, Al, Zn, K, F, Si, Mg, Cl ja Ti ja niiden yhdisteitä kuten oksideja; lääkeaineita, proteiineja, proteoglykaaneja, sokereita, kasvutekijöitä, hormoneja, entsyymejä, kollageenia ja antioksidantteja. Komposiitin käyttötarkoitus määrää luonnollisesti lisäaineen tai lisäaineiden valinnan.

Keksinnön mukainen komposiitti voi muodostaa tiiviin tai huokoisen kappaleen. Säätelemällä muovikomponentin ja bioaktiivisen komponentin välistä suhdetta saadaan haluttu komposiittirakenne. Muovikomponentin ja bioaktiivisen komponentin seossuhdetta voidaan säädellä varsin laajoissa rajoissa, eli bioaktiivisen komponentin pitoisuus voi vaihdella alueella 1...98 paino-% komposiitista. Jos bioaktiivisen komponentin pitoisuus on hyvin suuri, saadaan komposiittirakenne, jossa muovikomponentti muodostaa sideaineen bioaktiivisen komponentin partikkeleiden välille. Tällöin muodostuu jäykkä "sokeripalamainen" komposiitti. Jos bioaktiivisen komponentin pitoisuus on pienempi, eli alle 60 paino-%, saadaan muovimainen komposiitti, joka voi olla pehmeä tai joustava niin haluttaessa.

Komposiitti voi olla esimerkisi pinnoite, kalvo, verkko, lanka, kuitu, jauhe, tai kappale, kuten levy, pallo, putki, naula, sauva tai liima.

Keksinnön mukainen komposiitti voidaan myös valmistaa vasta käytön yhteydessä juuri ennen sen asettamista paikalleen kudokseen (esimerkiksi luuhun tai hampaaseen). Tällöin komposiitti valmistetaan "sulattamalla" muovikomponentti ja bioaktiivinen komponentti yhteen.

Keksinnön mukaisen komposiitin pohjalta voidaan myös valmistaa monikerroskomposiittia, kuten monikerroskalvoa siten, että eri kerrosten muovikomponentit plastisoituvat eri lämpötiloissa. Monikerroskomposiitti voi myös muodostua eri kerroksista, joiden muovikomponenttien biohajoavuus

vaihtelee. Monikerroskomposiitista valmistetun implantin pintakerros tai sen osa (toinen puoli, toinen reuna-alue) voi täten olla nopeammin tai hitaammin biohajoava kuin implantin syvemmät kerrokset.

Keksinnön mukainen komposiitti voi myös sisältää reikiä tai kanavia. Vaihtoehtoisesti voidaan komposiittiin tehdä ns. nutritiokanavia operaation aikana komposiitin asettamisen yhteydessä.

Sovellukset:

Keksinnön mukaisesta komposiitista voidaan valmistaa erilaisiin käyttötarkoituksiin soveltuvia tuotteita, joista voidaan esimerkkeinä mainita seuraavat ryhmät: luusto- tai rustosovellukset, hammas- ja leuka-alan sovellukset, rustopinnoitteet ja pehmytkudossovellukset. Luustosovelluksiin kuuluvat esimerkiksi luun tai ruston täyttömateriaali, putkiluiden korjaamiseen tarkoitettu tuote, silmäpohjan ja kasvoluiden korjauslevy, luusementti, liima tuotteen ja kudoksen tai kudosten kiinnittämiseen, implanttipinnoite, selkärangan korjauskappale ja kallolevy. Hammas- ja leuka-alan sovelluksista voidaan mainita väliaikainen hammaspaikkamateriaali, väliaikainen tai pysyvä hammasjuuren täytemateriaali, parodontaalinen tuote, hampaan poistokuoppaan asetettava tuote, hammassementti, väliaikainen hammassementti, väliaikainen kruunumateriaali, hammasimplanttipinnoite, purentaindeksikisko, kirurginen pasta ja jäljennösaine, joka voi olla esimerkiksi massa, rengas tai lanka, joka asetetaan ientaskuun. Lisäksi voidaan mainita tissue guiding -kalvo tai -putki, joka soveltuu luusto-, hammas- ja pehmytkudosalueille. Muista sovellutuksista voidaan edelleen mainita suojaliina, haavaliina, laastari sekä vaikuttavien aineiden ja muiden biologisten rakenteiden (autogeeninen ja allogeeninen luu) sekä lääkkeiden kantajaaine.

Lopputuotteen käyttötarkoituksen mukaan valitaan sopiva komposiitti tai komposiitit.

Bioaktiivisesta komponentista voidaan todeta, että bioaktiiviseen lasiin pohjautuva komposiitti sopii erityisen hyvin tuotteisiin, joiden ansiosta toivotaan tapahtuvan mineralisaatio (paikkamateriaalit, hampaan pinnoitteet, luutäytteet jne.), tai joiden toivotaan muodostavan luusidoksia luupuutosten rekonstruoimiseksi (luutäytteet, luusementit, erilaiset implantit jne.). Bioaktiiviseen geeliin pohjautuvat komposiitit soveltuvat erityisen hyvin lopputuotteisiin, joiden tarkoitus on luovuttaa vaikuttava aine (esimerkiksi kasvutekijä, hormoni, sytostaatti jne.) sairauden hoitoon tai ehkäisyyn. Geeliin perustuva komposiitti sopii myös käytettäväksi sovelluksissa, joissa mineralisaatiota ja luusidoksen muodostumista pidetään toivottavana. Geeliin pohjautuva komposiitti sopii myös tuotteiden vahvistamistarkoituksiin (geelikuitujen käyttö muovin vahvistamiseen, luupuikot, luunaulat ja luuruuvit, kalvot, jännekudos, paikka-aineet, luutäytteet yms.).

Muovimateriaalit voivat olla muovimaisia tai kumimaisia, ja niiden käyttöalueet jakautuvat siten, että muovimaisia tullaan käyttämään enimmäkseen täyttötarkoituksissa ja kumimaisia enimmäkseen luovutustarkoituksissa. Tietenkin jälleen kaikenlaiset seokset voivat tulla kyseeseen ja muovin valinta määräytyy enimmäkseen mekaanisten vaatimusten perusteella.

Esimerkkimateriaalina voidaan ottaa nivelnastan murtuman hoitoon käytettävä luutäytemateriaali. Nivelnastan murtuman hoidossa materiaalilta vaaditaan riittävää mekaanista lujuutta, jotta se voisi tukea kortikaaliluuta paranemisprosessin ajan. Sen pitää olla muotoiltavissa hohkaluuhun syntyneen kaviteetin täytteeksi. Sen pitää vapauttaa luun kasvua ja mineralisoitumista edistäviä epäorgaanisia ja/tai orgaanisia yhdisteitä ainakin paranemisprosessin ajan. Toisena esimerkkinä on putkiluun murtuma. Sen hoidossa voidaan materiaalilla kiinnittää (liimata) luunpäät murtumaraossa toisiinsa. Kolmas esimerkki on pienten murtumafragmenttien kiinnittäminen emoluuhun esim. rustomurtumassa.

Edellä esitetyistä vaatimuksista johtuen komposiittimateriaalin polymeerimatriisin pitää olla muovimainen ja sulaa juoksevaksi n. 42 °C:ssa. Sen hajoamisnopeuden tulisi olla yleensä noin 1 - 6 kuukautta, kohteesta riippuen 1 - 3 vuotta. Materiaalin toisena komponenttina pitää olla sol-gel -tuotettu Ca,P -pitoinen xerogeeli tai bioaktiivinen lasi granula- tai kuitumuodossa n. 60 - 70 p-% materiaalista, joka edesauttaa luun mineralisoitumista ja luun sitoutumista materiaaliin. Kolmantena komponenttina voi olla sol-gel -tuotettu luun kasvutekijää sisältävä xerogeeli, joka edesauttaa luuregeneraatiota luukaviteettiin ja muuhun luupuutokseen.

Seuraavasssa taulukossa (taulukko 1) nähdään keksinnön mukaiseen komposiittiin asetettavat vaatimukset lääkemuodon funktiona:

Taulukko 1

	ruiskutettava	implantoitava	neulamainen sauvamainen
polymeerimatriisi	kumimainen	muovimainen tai kumimainen	muovimainen
sulamislämpötila	polymeeri sulaa 45° C:ssa viskositeetti alhainen	lääkeaineesta riippuva sulamislämpötila	lääkeaineesta riippuva sulamislämpötila
geeli	ruiskukuivattua palloa	kappaleen muodosta riippuen partikkeli, kuitu tai monoliitti	kuitu

VALMISTUSESIMERKIT

Esimerkki 1

Matriisipolymeerin valmistus

Käytetyt kemikaalit:

Kopolymeerit valmistettiin ϵ-kaprolaktonimonomeerista (ϵ-

CL), > 99 % puhdas, Fluka Chemika nro 21510, erä 335334/1 794, ja D,L-laktidista (D,L-LA), Purac, erä DF386H. Katalyyttinä käytettiin tina(II)oktoaattia (Stannous 2-Ethylhexanoate; SnOct), 95 % puhdas, Sigma nro s-3252, erä 112H0248. Initiaattorina käytettiin glyserolia, 99,5 % puhdas, Fluka BioChemika nro 49767, erä 42489/2 1094.

Käytettyjen kemikaalien puhdistus ja säilytys:

Käytetyssä ϵ-kaprolaktonissa oli mukana molekyyliseuloja (lisätty 15.2.1995), ja pullo säilytettiin valolta suojattuna +23 °C:n lämpötilassa.

D,L-laktidi puhdistettiin uudelleenkiteyttämällä tolueenista (k.p. 110 °C) massasuhteessa 1:2 tolueeni/laktidi. Kuumaan tolueeniin liuennut laktidi kaadettiin pyörökolvista dekantterilasiin. Tolueeniin liuenneen laktidin annettiin uudelleenkiteytyä yön yli +23 °C:ssa. Suodatuksen jälkeen (keskinopea suodatinpaperi) kiteytynyt laktidi kuivattiin alennetussa paineessa 4 d +40 °C:ssa, paineen ollessa 4 mbar. Samat työvaiheet toistettiin. Polymeroinneissa käytettiin siten kahteen kertaan uudelleenkiteytettyä D,L-laktidia, jota säilytettiin eksikkaattorissa jääkaapissa +4 °C:n lämpötilassa.

Tinaoktoaatti ja glyseroli käytettiin sellaisinaan. Ne säilytettiin valolta suojattuina +23 °C:ssa.

Polymeroinnin esivalmistelut:

Edellisenä iltana polymeroinnissa käytettävä laktidi laitettiin tyhjiökaappiin +40 °C:n lämpötilaan 4 mbar paineeseen. Polymeroinnissa tarvittava kaksiosainen reaktori (tilavuudeltaan n. 0,7 l) koottiin. Reaktorin kokoamisen yhteydessä tarkistettiin siihen kuuluvan teflontiivisteen kunto. Reaktorin ylä- ja alaosan sulkeutuminen kunnolla varmistettiin käyttäen rautalangasta tehtyä suljinta. Reaktoriin kuuluvat hiokset siveltiin hioksen sisäpuolisil-

ta yläpinnoilta kevyesti hanarasvalla.

Polymerointi:

Reaktorin lämmitykseen käytetty öljyhaude säädettiin 140 °C:n lämpötilaan. Öljyn lämpötila vaihtelee polymeroinnin aikana 5 °C asetusarvon ylä- ja alapuolella. Laktidia punnittiin ensin noin 10 g pieneen dekantterilasiin (tarkkuus 0,0001 g). Laktidin päälle punnittiin tinaoktoaatti ja glyseroli pipetoimalla ne Pasteur-pipetillä. Tämän jälkeen dekantterilasi sisältöineen kaadettiin reaktion alaosaan. Loppuosa laktidista punnittiin toisella vaa'alla (tarkkuus 0,01 g). Laktidin päälle joko kaadettiin tai pipetoitiin ϵ-kaprolaktoni.

Reaktoriin lisättiin magneettisekoittaja ennen reaktiopuoliskojen sulkemista. Reaktori laitettiin hauteeseen, ja sekoitus säädettiin nopeuteen 250 min^{-1}. Reaktori huuhdeltiin argonilla (Aga, laatuluokka S, 99,99 %) n. 15 min ajan. Argon johdettiin reaktoriin glyserolilukon kautta. Lopuksi reaktorin ulkopinta vuorattiin foliolla. Sekoitusnopeus säädettiin uudelleen arvoon 125 min^{-1} syntyvän kopolymeerin alkaessa muuttua viskoosimmaksi.

Valmistetut kopolymeerit ja niiden analysointi:

Taulukossa 2 on esitetty yhteenveto suoritetuista ϵ-kaprolaktoni/D,L-laktidi (ϵ-CL/D,L-LA) - kopolymeroinneista ja tuotteiden analyysituloksista. Kaikissa polymeroinneissa lämpötila oli 140 °C ja polymerointiaika 24 h.

Taulukossa 2 esitetyt, geelisuodatuskromatografialla GPC määritetyt saatujen kopolymeerien moolimassa-arvot ovat lukukeskimääräinen moolimassa M_n, painokeskimääräinen moolimassa M_w sekä edellä mainittujen suhteena M_w/M_n saatava polydispersiteetti PD. Samassa taulukossa 2 esitetyt, differentiaalisella pyyhkäisykalorimetrialla (DSC) määritetyt saatujen polymerointituotteiden sulamislämpötila T_m.

Taulukko 2

Esimerkki	ε-CL/ D,L-LA-suhde	SnOct-pitoisuus mol/mol	Glys.pit. mol/mol	$\overline{M}_n$ 10^{-3} g/mol	$\overline{M}_w$ 10^{-3} g/mol	T_m °C
1	100/0	0,0001	0,005	45	60	56
2	80/20	0,0001	0,005	40	60	42
3	100/0	0,0001	0,25	4,3	5,2	35
4	60/40	0,0001	0,001	20	40	38

Polymeerin ominaisuudet:

Taulukossa 2 on esitetty tyypillisiä tuotepolymeerejä ja niiden ominaisuuksia:

GPC-mittaukset:

Moolimassa-arvojen mittauksissa GPC:llä näytteet valmistettiin siten, että 15 mg näytettä liuotettiin 10 ml:aan kloroformia. Kolonneina käytettiin Polymer Laboratories Ltd:n kolonneja huokoskooltaan 10^2 - 10^5 Å. Watersin valmistamalla RI- eli valon taitekertoimella toimivalla detektorilla analysoitiin näytteet ajoajan ollessa 55 min virtausnopeudella 1 ml/min. Näytteiden moolimassojen määrityksessä käytettiin Polymer Laboratories Ltd:n polystyreenistandardien (PS) avulla piirrettyä kokeellista kalibrointikäyrää. Koska kopolymeereille ei ole saatavissa kokeellisia Mark-Houwink' in yhtälön a- ja K-arvoja, taulukossa 2 olevat moolimassat eivät ole näytteiden absoluuttisia moolimassoja, vaan PS-standardeihin verrattuja, suhteellisia arvoja.

DSC-mittaukset:

DSC-mittauksissa 5 - 10 mg:n näytettä lämmitettiin nopeudella 10 °C/min kalorimetrikennossa. Jotta kaikkiin näytteisiin saatiin samanlainen terminen historia, näytteet

lämmitettiin sulamislämpötilansa yli +80 °C:seen ja jäähdytettiin n. -50 °C:seen. Toisen lämmityksen käyrästä rekisteröitiin T_m arvot, jotka on esitetty taulukossa 2.

Esimerkki 2

Komposiittimateriaalin valmistus

Esimerkin 1 mukaisesti valmistettua polymeeriä otettiin 20 g. Bioaktiivista lasia (tyyppi S53P4, viite 10), jonka keskimääräinen partikkelikoko on 300 µm, otettiin 20 g. Komponentit kaadettiin Brabender Co-Kneader -laitteen Kneteter-sekoituspäähän, jossa kierrosnopeus oli 50 rpm. Kneterpään lämpötila oli säädetty 55 °C:een ja sekoitusaika oli 15 min, jonka jälkeen sekoituspää avattiin ja homogenisoitunut materiaali otettiin talteen sulatilassa.

Lopputuotteena saatiin homogeeninen komposiittimateriaali, jonka biolasipitoisuus on 50 p-%. Komposiitti säilöttiin kaasutiiviiseen astiaan typpisuojakaasun alle.

Yllä mainitut keksinnön suoritusmuodot ovat vain esimerkkejä keksinnön mukaisen idean toteuttamisesta. Alan asiantuntijalle on selvää, että keksinnön erilaiset sovellutusmuodot voivat vaihdella jäljempänä esitettävien patenttivaatimusten puitteissa.

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PATENTTIVAATIMUKSET

1. Lääketieteelliseen, erityisesti kirurgiseen tai terapeuttiseen käyttöön tarkoitettu komposiitti, tunnettu siitä, että se käsittää
- lämpötila-alueella -10 °C...+100°C plastisoitavissa olevan termoplastisen muovikomponentin, joka oleellisesti koostuu hydroksihapoista tai hydroksihappojohdannaisista johdetuista rakenneyksiköistä, ja jonka moolimassa on alueella 10 000 - 1 000 000 g/mol, ja joka hajoaa elimistössä tyypillisesti muutamasta päivästä useampiin vuosiin pituisessa ajassa ja joka kiinteässä muodossaan on mekaanisesti luja muovimainen tai kumimainen aine, sekä
- bioaktiivisen komponentin, joka on bioaktiivinen lasi, bioaktiivinen xerogeeli, bioaktiivinen keraami, koralli tai koralliperäinen tuote, tai bioaktiivinen lasikeraami.

2. Patenttivaatimuksen 1 mukainen komposiitti, tunnettu siitä, että muovikomponentti on plastisoitavissa lämpötila-alueella 5 °C...70 °C, edullisesti lämpötila-alueella 37 °C...55 °C.

3. Patenttivaatimuksen 1 tai 2 mukainen komposiitti, tunnettu siitä, että plastisoitu muovikomponentti on muovailtavissa vielä tietyn ajan sen jälkeen, kun komposiitin lämpötila on laskettu lämpötilaan, joka on tuntuvasti alempi kuin mainitun muovikomponentin kovettumislämpötila.

4. Patenttivaatimuksen 1, 2 tai 3 mukainen komposiitti, tunnettu siitä, että muovikomponentti on säädellysti biohajoava aikavälillä 1 viikko - 3 vuotta.

5. Patenttivaatimuksen 4 mukainen komposiitti, tunnettu siitä, että rakenneyksikkö on L-, D- tai DL-maitohappo; L-, D- tai DL-laktidi; tai epsilon-kaprolaktoni.

6. Patenttivaatimuksen 5 mukainen komposiitti, tunnettu siitä, että muovikomponentti on L-laktidi- ja epsilon-

kaprolaktoni-rakenneyksikköihin perustuva sekapolymeeri.

7. Patenttivaatimuksen 6 mukainen komposiitti, tunnettu siitä, että sekapolymeerin koostumus on alueella

$$\frac{\text{epsilon-kaprolaktoni}}{\text{L-laktidi}} = 2/98 \ldots 98/2$$

8. Patenttivaatimuksen 7 mukainen komposiitti, tunnettu siitä, että

$$\frac{\text{epsilon-kaprolaktoni}}{\text{L-laktidi}} = 4 : 1$$

9. Patenttivaatimuksen 8 mukainen komposiitti, tunnettu siitä, että sekapolymeerin moolimassa on noin 30 000 - 300 000 g/mol.

10. Jonkin edellisistä patenttivaatimuksista mukainen komposiitti, tunnettu siitä, että bioaktiivinen komponentti esiintyy komposiitissa erillisinä partikkeleina.

11. Patenttivaatimuksen 10 mukainen komposiitti, tunnettu siitä, että erilliset partikkelit ovat kuituja, huokoisia kappaleita, mikropartikkeleita tai lasipalloja.

12. Jonkin edellisistä patenttivaatimuksista mukainen komposiitti, tunnettu siitä, että muovikomponentti ja/tai bioaktiivinen komponentti sisältää yhden tai useamman lisäaineen.

13. Jonkin edellisistä patenttivaatimuksista mukainen komposiitti, tunnettu siitä, että muovikomponentti ja bioaktiivinen komponentti muodostavat tiiviin kappaleen.

14. Jonkin patenttivaatimuksista 1 - 12 mukainen komposiitti, tunnettu siitä, että muovikomponentti muodostaa huokoisen kappaleen.

15. Seos, joka on tarkoitettu jonkin patenttivaatimuksista 1 - 14 mukaisen komposiitin valmistamiseksi, tunnettu siitä, että seoksen muovikomponentti ja bioaktiivinen komponentti ovat jauhemuodossa.

16. Jonkin patenttivaatimuksista 1 - 14 mukaisesta komposiitista valmistettu pinnoite, kalvo, verkko, jauhe, kuitu, lanka, liima tai kappale, kuten levy, pallo, putki, naula tai sauva.

17. Jonkin patenttivaatimuksista 1 - 14 mukaisen komposiitin käyttö jonkin seuraavista tuotteista valmistukseen:
- luusto- tai rustosovellus, kuten luun tai ruston täyttömateriaali, putkiluiden korjaamiseen tarkoitettu tuote, silmäpohjan tai kasvoluiden korjauslevy, luusementti, liima tuotteen ja kudoksen tai kudosten kiinnittämiseen, implanttipinnoite, selkärangan korjauskappale ja kallolevy,
- hammas- ja leuka-alan sovellus, kuten väliaikainen hammaspaikkamateriaali, väliaikainen tai pysyvä hammasjuuren täytemateriaali, parodontaalinen tuote, hampaan poistokuoppaan asetettava tuote, hammassementti, väliaikainen hammassementti, väliaikainen kruunumateriaali, hammasimplanttipinnoite, purentaindeksikisko, kirurginen pasta ja jäljennösaine, joka voi olla esimerkiksi ientaskuun sovitettava massa, rengas tai lanka,
- rustopinnoite,
- tissue guiding -kalvo tai -putki,
- suojaliina, haavaliina tai laastari,
- vaikuttavan aineen, kuten lääkkeen kantaja-aine tai muun biologisen rakenteen kantaja-aine.

(57) TIIVISTELMÄ

Keksinnön kohteena on lääketieteelliseen, erityisesti kirurgiseen tai terapeuttiseen käyttöön tarkoitettu komposiitti. Keksinnön mukaan komposiitti käsittää
- lämpötila-alueella -10 °C...+100°C plastisoitavissa olevan termoplastisen muovikomponentin, joka oleellisesti koostuu hydroksihapoista tai hydroksihappojohdannaisista johdetuista rakenneyksiköistä, ja jonka moolimassa on alueella 10 000 - 1 000 000 g/mol, ja joka hajoaa elimistössä tyypillisesti muutamasta päivästä useampiin vuosiin pituisessa ajassa ja joka kiinteässä muodossaan on mekaanisesti luja muovimainen tai kumimainen aine, sekä
- bioaktiivisen komponentin, joka on bioaktiivinen lasi, bioaktiivinen xerogeeli, bioaktiivinen keraami, koralli tai koralliperäinen tuote, tai bioaktiivinen lasikeraami.

Keksintö koskee myös uuden komposiitin käyttöä ja siitä valmistettuja tuotteita.